WHAT IS CLAIMED IS:

1. A method of obtaining a bacterium comprising a nucleic acid sequence encoding a binding protein capable of binding a target ligand comprising the steps of:

(a) providing a Gram negative bacterium comprising a nucleic acid sequence encoding a candidate binding protein, wherein said binding protein is expressed in soluble form in said bacterium;

(b) contacting said bacterium with a labeled ligand capable of diffusing into said bacterium; and

(c) selecting said bacterium based on the presence of said labeled ligand within the bacterium, wherein said ligand and said candidate binding protein are bound in said bacterium.

2. The method of claim 1, further defined as a method of obtaining a nucleic acid sequence encoding a binding protein capable of binding a target ligand, the method further comprising the step of:

(d) cloning said nucleic acid sequence encoding said candidate binding protein.

3. The method of claim 1, wherein said binding protein is expressed in soluble form in the periplasm of said bacterium.

4. The method of claim 3, wherein said nucleic acid sequence encoding a candidate binding protein is further defined as operably linked to a leader sequence capable of directing expression of said candidate binding protein in said periplasm.

5. The method of claim 1, wherein said Gram negative bacterium is an *E. coli* bacterium.

6. The method of claim 1, further defined as comprising providing a population of Gram negative bacteria.

7. The method of claim 6, wherein said population of bacteria is further defined as collectively capable of expressing a plurality of candidate binding proteins.

8. The method of claim 7, wherein said population of bacteria is obtained by a method comprising the steps of:

(a) preparing a plurality DNA inserts which collectively encode a plurality of different potential binding proteins, and

(b) transforming a population of Gram negative bacteria with said DNA inserts.

9. The method of claim 6, wherein said population of Gram negative bacteria is contacted with said labeled ligand.

10. The method of claim 1, wherein said candidate binding protein is further defined as an antibody or fragment thereof.

11. The method of claim 1, wherein said candidate binding protein is further defined as a binding protein other than an antibody.

12. The method of claim 1, wherein said candidate binding protein is further defined as an enzyme.

13. The method of claim 1, wherein said candidate binding protein is further defined as not capable of diffusing out of said periplasm in intact bacteria.

14. The method of claim 1, wherein said labeled ligand comprises a peptide.

15. The method of claim 1, wherein said labeled ligand comprises a polypeptide.

16. The method of claim 1, wherein said labeled ligand comprises an enzyme.

17. The method of claim 1 where said labeled ligand comprises a nucleic acid.

18. The method of claim 1, wherein said labeled ligand is further defined as comprising a molecular weight of less than about 20,000 Da.

19. The method of claim 1, wherein said labeled ligand is further defined as comprising a molecular weight of less than about 5,000 Da.

20. The method of claim 1, wherein said labeled ligand is further defined as comprising a molecular weight of greater than 600 Da and less than about 30,000 Da.

21. The method of claim 1, wherein said labeled ligand is further defined as fluorescently labeled.

22. The methods of claim 1, wherein said nucleic acid encoding a candidate binding protein if further defined as capable of being amplified following said selection.

23. The method of claim 1, further comprising treating said bacterium to facilitate said diffusing into said periplasm.

24. The method of claim 23, comprising treating the bacterium with hyperosmotic conditions.

25. The method of claim 23, comprising treating the bacterium with physical stress.

26. The method of claim 24, comprising treating the bacterium with a phage.

27. The method of claim 1, wherein said bacterium is grown at a sub-physiological temperature.

28. The method of claim 27, wherein said sub-physiological temperature is about 25°C

29. The method of claim 1, further comprising removing labeled ligand not bound to said candidate binding protein.

30. The method of claim 1, wherein said selecting comprises FACS.

31. The method of claim 1, wherein said selecting comprises magnetic separation.

32. The method of claim 1, wherein said ligand and said candidate binding protein are reversibly bound in said periplasm.

33. A method of obtaining a bacterium comprising a nucleic acid sequence encoding a catalytic protein catalyzing a chemical reaction involving a target substrate, the method comprising the steps of:

(a) providing a Gram negative bacterium comprising a nucleic acid sequence encoding a candidate catalytic protein, wherein said catalytic protein is expressed in soluble form in said bacterium;

(b) contacting said bacterium with a target substrate capable of diffusing into said bacterium, wherein said candidate catalytic protein catalyzes a chemical reaction involving said target substrate and wherein said chemical reaction yields at least a first substrate product; and

(c) selecting said bacterium based on the presence of said first substrate product.

34. The method of claim 33, further defined as a method of obtaining a nucleic acid sequence encoding a catalytic protein catalyzing a reaction with a target substrate, the method further comprising the step of:

(d) cloning said nucleic acid sequence encoding said candidate catalytic protein.

35. The method of claim 33, wherein said candidate catalytic protein is expressed in soluble form in the periplasm of said bacterium.

36. The method of claim 35, wherein said nucleic acid sequence encoding a candidate catalytic protein is further defined as operably linked to a leader sequence capable of directing expression of said candidate catalytic protein in said periplasm.

37. The method of claim 33, wherein said Gram negative bacterium is an *E. coli* bacterium.

38. The method of claim 33, further defined as comprising providing a population of Gram negative bacteria.

39. The method of claim 38, ~~wherein~~ said population of bacteria is further defined as collectively capable of expressing a plurality of candidate catalytic proteins.

40. The method of claim 39, wherein said population of bacteria is obtained by a method comprising the steps of:

(a) preparing a plurality DNA inserts which collectively encode a plurality of different candidate catalytic proteins, and

(b) transforming a population of Gram negative bacteria with said DNA inserts.

41. The method of claim 38, wherein said population of Gram negative bacteria is contacted with said target substrate.

42. The method of claim 33, wherein said candidate catalytic protein is further defined as an enzyme.

43. The method of claim 33, wherein said candidate catalytic protein is further defined as not capable of diffusing out of said periplasm.

44. The method of claim 33, wherein said target substrate comprises a molecule containing a scissile amide bond.

45. The method of claim 33, wherein said target substrate comprises a polypeptide.

46. The method of claim 33, wherein said target substrate comprises a molecule containing a scissile carboxylic ester bond.

47. The method of claim 33, wherein said target substrate comprises a nucleic acid.

48. The method of claim 33, wherein said target substrate comprises a molecule containing a scissile phosphate ester bond.

49. The method of claim 33, wherein said target substrate comprises a molecule containing a scissile sulfonate ester bond.

50. The method of claim 33, wherein said target substrate comprises a molecule containing a scissile carbonate ester bond.

51. The method of claim 33, wherein said target substrate comprises a molecule containing a scissile carbamate bond.

52. The method of claim 33, wherein said target substrate comprises a molecule containing a scissile thioester bond.

53. The method of claim 33, wherein said target substrate is further defined as comprising a molecular weight of less than about 20,000 Da.

54. The method of claim 33, wherein said target substrate is further defined as comprising a molecular weight of less than about 5,000 Da.

55. The method of claim 33, wherein said target substrate is further defined as comprising a molecular weight of less than about 3,000 Da.

56. The method of claim 33, wherein said target substrate is further defined as comprising a molecular weight of greater than about 600 Da and less than about 30,000 Da.

57. The method of claim 33, wherein said first substrate product is further defined as capable of being detected based on the presence of a fluorescent signature.

58. The method of claim 57, wherein said fluorescent signature is absent in said target substrate.

59. The method of claim 58, wherein said fluorescent signature is produced by catalytic cleavage of a scissile bond.

60. The method of claim 59, further defined as comprising use of a FRET system, said FRET system comprising a fluorophore bound by a scissile bond to at least a first molecule capable of quenching the fluorescence of said fluorophore, wherein cleavage of said scissile bond allows said first molecule to diffuse away from the fluorophore and wherein the fluorescence of said fluorophore becomes detectable.

61. The method of claim 60, wherein the fluorophore comprises a positive charge allowing the fluorophore to remain associated with the bacterium.

62. The method of claim 57, wherein said target substrate is further defined as comprising a latent fluorescent moiety capable of being released by said chemical reaction involving said target substrate.

63. The method of claim 62, wherein the latent fluorescent moiety released by said cleavage possesses an overall positive charge allowing said moiety to remain associated with the bacterium following said cleavage.

64. The method of claim 57, further defined as comprising labeling said target substrate with a fluorescent pH probe capable of being detected upon a change in pH associated with said chemical reaction involving said target substrate.

65. The method of claim 64, wherein said fluorescent pH probe possesses an overall positive charge allowing said fluorescent pH probe to remain associated with the bacterium following said chemical reaction involving said target substrate.

66. The method of claim 33, wherein said bacterium is further defined as viable following said selecting.

67. The method of claim 33, further comprising treating said bacterium to facilitate said diffusing into said periplasm.

68. The method of claim 67, comprising treating the bacterium with hyperosmotic conditions.

69. The method of claim 67, comprising treating the bacterium with physical stress.

70. The method of claim 67, comprising treating the bacterium with a phage.

71. The method of claim 33, wherein said bacterium is grown at a sub-physiological temperature.

72. The method of claim 71, wherein said sub-physiological temperature is about 25°C.

73. The method of claim 33, wherein said selecting comprises FACS.

74. The method of claim 33, wherein said selecting comprises magnetic separation.